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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,296	11/28/2000	Paul W. Doetsch	25-98A	4866

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GREENLEE, WINNER AND SULLIVAN, P.C.
Suite 201
5370 Manhattan Circle
Boulder, CO 80303

EXAMINER	
WALICKA, MALGORZATA A	

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 10/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/724,296	DOETSCH ET AL.	
	Examiner	Art Unit	
	Malgorzata A. Walicka	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 June 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21-25* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21-25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

The Amendment under 37 C.F.R. 1.111 filed on June14, 2004 is acknowledged. None of the claims has been canceled or amended. Claims 21-25 are pending in the application and are the subject of this Office Action.

Office Action

1. Objections

Objection to claim 21 is withdrawn.

2. Rejections

2.2. 35 USC section 103

Claims 21- 24 remain rejected for reasons indicated in the previous Office Action that are repeated bellow.

He claims are rejected under 35 U.S.C. 102(b) as being anticipated by Takao et al. (Nucleic Acid Res. **1996**, 24, 1267-1271) in view of Ford et al. (Fusion Tails for the Recovery and Purification of Recombinant Proteins, Protein expression and purification, **1991**, 2, 95-107.

Claims 21-22 and 24 are directed to the method for cleavage of a double–stranded DNA molecule containing a distorted structure wherein the distortion is caused by UV irradiation, a photoproduct, when the cleavage enzyme is set forth by SEQ ID NO: 4 consisting of truncated *S. pombe* UVDE endonuclease amino acids residues 230-828 and when the enzyme is at least 90% pure.

Claim 23 is directed to the method for cleavage of a double–stranded DNA molecule containing a distorted structure wherein the distortion is caused by UV

irradiation, a photoproduct, when the cleavage enzyme is set forth by SEQ ID NO: 6 consisting of glutathione-S-transferase leader followed by amino acids residues 230-828 of S. *pombe* UVDE endonuclease, i.e. a fusion of GST and truncated sequence and S. pombe UVDE endonuclease.

Takao et al. cloned *S. pombe* UVDE endonuclease gene consisting of 599 amino acids, identical to amino acids 230-828 of SEQ ID NO: 2 of the instant application. Takao et al. teach the method of incision of double stranded DNA distorted by irradiation with UV, containing 6-4 photoproduct and cyclobutane pyrimidine dimers, using their UVDE endonuclease, page 1268, left column; see subtitles *Plasmid nicking assay* and *Incision assay using synthetic oligonucleotides*. Takao et al. expressed the enzyme in *E. coli* and purified it using as the first step heparin-Sepharose column and subsequently blue-Sepharose, page 1269, left column, line 11. However, they experienced difficulties in purification of a stable protein from *E. coli.* Takao et al. also reported successful expression of UVDE gene in S. cerevisiae; page 1271, right column, line 20.

Takao et al. do no teach, however, how to efficiently recover and purify the UVDE enzyme expressed in any microorganism.

Ford et al. teach that making a fusion protein consisting of glutathione-S-transferase tail (GST) and an enzyme of interest, page 96, right column, line 29, enables efficient recovery and purification using the affinity column containing immobilized glutathione. The GST can be subsequently cleaved out of the enzyme by thrombin, if the fusion protein is not active.

It would have been obvious to one having ordinary skill in the art at the time of invention to have the method of DNA cleavage of Takao et al. and to modify the expression and purification of UVDE endonuclease as taught by Ford.

The motivation for the modification would be to have a large quantity of pure and stable enzyme necessary for the method. The motivation is provide by Ford et al. who state, "On a lab scale, fusion tail recovery systems are powerful and elegant tools for one –step recovery and purification of recombinant proteins or identification of proteins encoded by cloned cDNAs. On an industrial scale, fusion tail technology can be used in the recovery and purification of both higher-cost pharmaceuticals and lower-to medium –cost enzymes."

The expectation of success in obtaining stable and pure truncated S. pombe UVDE is very high because of well-developed and routine use of the glutathione-S-transferase fusion protein, which may be used with (SEQ ID NO: 4) or without cleavage (SEQ ID NO: 6) of the GST leader by trypsin.

Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made, and was as a whole *prima facie* obvious.

In their response to the above rejection Applicants state on page 5, line 12, "the cited reference [Takao] does not teach a GST-truncated UVDE fusion protein (SEQ iD NO:6), as recited in claims 21 and 23."

The examiner agrees with this argument. This is the very reason for which the rejection under 35 USC, section 102, cannot be used, and the invention is rejected under 35 USC, section 13.

2.3. 35 USC, section 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2.3.1. Lack of written description- new rejection

The rejection of claims claims 21-24 is not withdrawn. The claims are rejected for reasons stated in the previous Office Action that are repeated bellow.

Claims 21-24 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are directed to the method for cleavage of a double stranded DNA molecule containing a platinum diadduct, intercalated molecule or alkylation of a nucleotide, wherein the cleaving enzyme is truncated *S. pombe* UVDE. The claims are

directed to a genus of methods of cleaving double stranded DNA containing a genus of DNA lesions comprising the following subgenera:

a) a platinum diadduct,

b) an intercalating molecule, and

c) alkylation of a nucleotide.

Neither the subgenera of lesions nor the specific activity of the S. pombe truncated UVDE directed to these subgenera of lesions are sufficiently described.

The disclosure teaches that the truncated S. pombe UVDE endonuclase is specific towards one form of platinum diadduct, platinum-DNA GG diadduct, however, the specification fails to teach that the enzyme is active towards other platinum –DNA diadducts.

The disclosure is silent as to any intercalating molecule, which, when intercalated into the double stranded DNA, is recognized by the truncated S. pombe UVDE endonuclase. This is a complete lack of written description.

The disclosure is silent as to any alkylation of a nucleotide which is recognized by the truncated S. pombe UVDE endonuclase. This is a complete lack of written description.

Given the lack of disclosure of activities of truncated S. pombe UVDE towards certain lesions as stated above, Applicants have failed to sufficiently describe the invention of claim 21-24 in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

Claim 25 is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim is directed to a genus of methods for cleavage of a double stranded DNA molecule containing lesions wherein the cleaving enzymes are set forth by SEQ ID NO: 36 (*Neurospora crassa* UVDE), SEQ ID NO: 37 (*Bacillus subtilis* homolog of UVDE), SEQ ID NO: 38 (*Homo sapiens* MED1 endonuclease specific for repair of the mismatched nucleotides) and SEQ ID NO: 39 (*Deinococcus radiodurans* homolog of UVDE). The claim is directed to a genus of methods of cleaving double stranded DNA containing a genus of DNA lesions comprising the following subgenera:

a) an abasic site,

b) mismatched nucleotide pairing,

c) a platinum diadduct,

d) an insertion deletion loop,

e) alkylation of a nucleotide, and

f) the presence of uracil residue,

with the provisio that when the endonuclease comprises the amino acid sequence of SEQ ID NO: 38, the distorted structure does not result from mismatched nucleotides.

The specification fails to teach that the polypeptides set forth by SEQ ID NOs: 36-39 have endonucleolytic activity directed to the lesions a) - f) above. The

disclosure teaches the specificity of S. pombe UVDE, or its truncated form, towards an abasic site, mismatched nucleotide, platinum–DNA GG diaduct, an insertion deletion loop of less than 5 nucleotides, uracil and diuracil. Thus, claim 25 suffers from a complete lack of written description regarding the claimed specificities of polypeptides of SEQ ID NO: 36-39. The examiner emphasizes that this is not the lack of enablement, because on skilled in the art, using the guidance given by the specification, could determine whether polypeptides of SEQ ID NO: 36-39 have the endolytic activities directed to lesion listed under a) – d) and f).

In addition, **the provisio** "when the endonuclease comprises the amino acid sequence of SEQ ID NO: 38, the distorted structure does not result from mismatched nucleotides" **is a new matter**. No such provision was made in the specification and claims as originally filed.

Furthermore, the disclosure teaches how to measure specificity toward only one, and not any, platinum diadduct, i.e., towards platinum-DNA GG diadduct. The specification does not teach and does not provide evidence that any of the enzymes of SEQ ID NOs:36-39 have the activity towards any alkylated nucleotide, thus the claim is completely lacking written description.

Given the lack of disclosure activities of the enzymes towards certain lesions as stated above, Applicants have failed to sufficiently describe the invention of claim 25 in such full, clear, concise and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention when the application was filed.

2.3.2. Lack of enablement

Rejection of claims 21-25 made in the previous office Action is not withdrawn. The claims are relected for reasons the are repeated bellow.

Claims 21-25 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to the method for cleavage of a double – stranded DNA molecule containing any alkylation of a nucleotide or/and to the method for cleavage of double-stranded DNA molecule containing any intercalated molecule. The specification, however, fails to teach any DNA lesion which is an alkylation of a nucleotide or any DNA lesion which is caused by intercalation of any DNA intercalating molecule. For that reason, the specification fails to teach that any of the enzymes, SEQ ID NOs: 4, 6, and 36-39 has an activity toward said lesions. Therefore, to make and use the claimed invention undue experimentation is necessary.

Factors to be considered in determining whether undue experimentation is required, are summarized *In re* Wands [858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)]. The Wands factors are: (a) the quantity of experimentation necessary, (b) the amount of direction or guidance presented, (c) the presence or absence of working example, (d) the nature of the invention, (e) the state of the prior art, (f) the relative skill of those in the art, (g) the predictability or unpredictability of the art, and (h) the breadth of the claim.

The nature and breadth of the claimed invention encompasses a genus of methods for cleavage a damaged DNA molecule by six enzymes, when the scope of the chemical lesions encompasses any alkylation of a nucleotide out of large number of known and thus far unidentified alkylations, as well as any lesion caused by intercalation of any out of a large number of known and unidentified intercalating molecules. The art of the determination of the endolytic activites of repair enzymes is well developed and skills of artisans high. However, while enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed so that the methods used the claimed endonucleolytic activities. The unpredictability of specificity of polypeptides of SEQ ID NO: 4, 6, and 36-39 towards a specific alkylation or intercalation is high, thus the experimentation left to those skilled in the art has a low probability of success absent the detailed guidance regarding the structure of alkylation and intercalation.

The disclosure fails to provide such guidance regarding which of alkylated nucleotides and intercalations of which intercalating molecules are to be used as the substrates-lesions for repair enzymes of SEQ ID NO: 4, 6, and 36-39. Without a further guidance on the part of Applicants with regards to the structure of the generic lesions recited by the claims one skilled in the art is forced to improperly extensive and undue experimentation.

It is noted that in their traverse of the above rejection Applicants do not address the rejection of claim 25 for new matter.

3. Conclusion

No claim is in conditions for allowance, however the claims contain the allowable subject matter. The following is the examiner reason for allowable subject matter.

Applicants disclose novel activities of the truncated form of the S. pombe endonuclease of SEQ ID NOs: 4 and 6. Said activities are used in the method of cleavage a double–stranded DNA containing the following lesions: **Dewar isomer of 6-4 photoproduct, abasic site, uracil, dihydrouracil (not recited by the claims), platinum-DNA GG diadduct, mismatched nucleotide, and loop of less than 5 nucleotides.**

As allowable subject matter has been indicated, applicant's reply must either comply with all formal requirements or specifically traverse each requirement not complied with. See 37 CFR 1.111(b) and MPEP § 707.07(a).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the

shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Malgorzata A. Walicka, Ph.D., whose telephone number is (703) 305-7270. The examiner can normally be reached Monday-Friday from 10:00 a.m. to 4:30 p.m.

If attempts to reach examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, Ph.D. can be reached on (703) 308-3804. The fax phone number for this Group is (703) 305-3014.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionists whose telephone number is (703) 308-0196.

Malgorzata A. Walicka, Ph.D.
Art Unit 1652
Patent Examiner

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600